Answer 1:

Bibliographic Information

Acridine derivatives activate p53 and induce tumor cell death through Bax. Wang, Wenge; Ho, William C.; Dicker, David T.; MacKinnon, Colin; Winkler, Jeffrey D.; Marmorstein, Ronen; El-Deiry, Wafik S. Departments of Medicine, Genetics, Pharmocology and Cancer Center; University of Pennsylvania School of Medicine, The University of Pennsylvania, Philadelphia, PA, USA. Cancer Biology & Therapy (2005), 4(8), 893-898. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:388820 AN 2006:480440 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

CP-31398 activates wild-type p53 by a novel mechanism that does not involve phosphorylation of the amino-terminus of p53 and disassocn. of MDM2. To identify more potent CP-31398-like p53 activators, we synthesized 4 acridine derivs. with a similar structure to CP-31398. These four compds. induced strong p53 transcription in cells with wild-type p53. We also found that several randomly chosen acridine derivs., including 9-aminoacridine, amsacrine, quinacrine and acridine orange, induced p53 transcriptional activity. All these acridine derivs. stabilized p53 protein by blocking its ubiquitination, without phosphorylation of ser15 or ser20 on p53. Furthermore, acridine derivs. induced p53-dependent cell death. Knockout of Bax, a p53 target and a key cell death inducer in both intrinsic and extrinsic apoptotic pathways, blocked acridine derivs. from inducing cell death. In addn., in vivo delivery of quinacrine and amsacrine induced p53 transcriptional activity in tumor xenografts. Our results reveal that DNA-interacalating acridine derivs. can induce p53 stabilization by a manner similar to CP-31398. These findings provide insights into p53 regulation in response to DNA intercalating drugs and may assist new anti-cancer drug design.

Answer 2:

Bibliographic Information

Experimental solid tumor activity of N-[2-(dimethylamino)ethyl]acridine-4-carboxamide. Baguley, Bruce C.; Zhuang, Li; Marshall, Elaine. School of Medicine, University of Auckland, Auckland, N. Z. Cancer Chemotherapy and Pharmacology (1995), 36(3), 244-8. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 123:132181 AN 1995:724500 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The activity of the title compd. (DACA), a topoisomerase II inhibitor, was assessed against advanced (5-mm diam.) s.c. colon 38 adenocarcinomas in BDF1 mice, using tumor-growth delay as an end point. Its activity was related pos. to the total dose given and neg. to the total duration of the dose schedule. Adoption of a split-dose i.p. administration schedule or slow i.v. infusion allowed the administration of large doses without toxicity. The activity of DACA was comparable to that of 5-fluorouracil and superior to that of doxorubicin, cyclophosphamide and the exptl. amsacrine analog CI-921. Mitoxantrone, amsacrine, etoposide, teniposide and daunorubicin showed minimal activity. DACA also demonstrated significant activity against the NZM3 human melanoma cell line growing as a xenograft in athymic mice.

Answer 3:

Bibliographic Information

Phase II perclinical drug screening in human tumor xenografts: a first European multicenter collaborative study. Boven, Epie; Winograd, Benjamin; Berger, Dietmar P.; Dumont, M. Patrick; Braakhuis, Boudewijn J. M.; Fodstad, Oystein; Langdon, Simon; Fiebig, Heiner H. Dep. Med. Oncol., Free Univ. Hosp., Amsterdam, Neth. Cancer Research (1992), 52(21), 5940-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 118:134 AN 1993:134 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In a European joint project carried out in 6 labs., a disease-oriented program was set up consisting of a panel of 7 tumor types, each represented by 4 to 8 different human tumor lines, for secondary screening of promising anticancer drugs. Human tumor lines were selected on the basis of differences in histol., growth rate, and sensitivity to conventional cytostatic agents. Xenografts were grown s.c. in nude mice, and treatment was started when tumors reached a mean diam. of 6 mm in groups of mice where at least 6 tumors were evaluable. Drugs were given at the max. tolerated dose. For evaluation of drug efficacy, median tumor growth curves were drawn, and specific growth delay and treated/control × 100% were calcd. Doxorubicin (8 mg/kg i.v. days 1 and 8) was effective (treated/control <50%, and specific growth delay >1.0) in 0 of 2 breast cancers, 1 of 3 colorectal cancers, 2 of 5 head and neck cancers, 3 of 6 non-small cell lung cancers, 4 of 6 small cell lung cancers, 0 of 3 melanomas, and 3 of 6 ovarian cancer lines. Amsacrine (8 mg/kg i.v. days 1 and 8) was not effective, while datelliptium (35 mg/kg i.p. days 1 and 8) was active against 2 of 6 small cell lung cancer lines. Brequinar sodium (50 mg/kg i.p. days 1-5) showed efficacy in 4 of 5 head and neck cancers, 5 of 8 non-small cell lung cancers, and 4 of 5 small cell lung cancer lines. The project has been shown to be a feasible approach. Clin. activity for doxorubicin and inactivity for amsacrine against solid tumor types was confirmed in the human tumor xenograft panel. Addnl. anticancer drugs will be studied in the European joint project to further define the reliability of this novel, promising screening approach.

Answer 4:

Bibliographic Information

Antitumor activity and cross-resistance of carmethizole hydrochloride in preclinical models in mice. Waud, William R.; Plowman, Jacqueline; Harrison, Steadman D., Jr.; Dykes, Donald J.; Anderson, Wayne K.; Griswold, Daniel P. Jr. South. Res. Inst., Birmingham, AL, USA. Cancer Chemotherapy and Pharmacology (1992), 30(4), 261-6. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 117:225842 AN 1992:625842 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Carmethizole hydrochloride [1-methyl-2-methylthio-4,5-bis(hydroxymethyl)imidazole-4',5'-bis(N-methylcarbamate) hydrochloride, NSC 602 668; carmethizole] is a new antitumor drug that has shown relatively broad activity in initial evaluations against several murine tumors and human tumor xenografts in vivo. The present studies were designed to address questions about carmethizole's activity against established disease, its activity on different treatment schedules, and the extent of its cross-resistance with established drugs. Human MX-1 mammary carcinoma, human NCI-H82 small-cell lung carcinoma, and human LOX amelanotic melanoma xenografts in athymic mice were used to det. the drug's activity against established disease; the NCI-H82 lung-tumor xenograft in athymic mice was used to explore its schedule dependence; and a series of drug-resistant murine leukemias provided an in vivo cross-resistance profile. When injected i.p., carmethizole exhibited antitumor activity against advanced-stage s.c. MX-1 mammary, s.c. NCI-H82 lung, and i.p. LOX melanoma xenografts and was as effective against established disease (MX-1 and LOX) as it was against early-stage disease (no data are available for early-stage NCI-H82). The therapeutic effect of carmethizole was not route-dependent, as was evidenced by the similar delays obsd. in tumor growth following i.p. and i.v. administration. The use of a split-dose schedule on a single day instead of one bolus injection yielded an increase in the total dose delivered, resulting in an increased delay in tumor growth. Murine leukemias resistant to vincristine (VCR), amsacrine (AMSA), or methotrexate (MTX) were not cross-resistant to carmethizole.

However, murine leukemias resistant to doxorubicin (ADR), melphalan (L-PAM), cisplatin (DDPt), 1-β-D-arabinofuranosylcytosine (ara-C), and 5-fluorouracil (5-FU) were cross-resistant to carmethizole, suggesting that patients who have previously been treated with any of these agents might be less likely to respond to carmethizole than those who have had no opportunity to develop resistance to any of these compds. The authors anticipate that the information derived from these studies may be useful in the design of clin. trials of carmethizole and may stimulate addnl. basic research on the mechanism of action of this new agent.

Answer 5:

Bibliographic Information

Preclinical antitumor activity of penclomedine in mice: cross-resistance, schedule dependence, and oral activity against

tumor xenografts in brain. Harrison, Steadman D., Jr.; Plowman, Jacqueline; Dykes, Donald J.; Waud, William R.; Griswold, Daniel P., Jr. South. Res. Inst., Birmingham, AL, USA. Cancer Research (1991), 51(8), 1979-83. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 115:41434 AN 1991:441434 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Penclomedine is 3,5-dichloro-2,4-dimethoxy-6-(trichloromethyl)pyridine (NSC 338720), an α-picoline deriv. with oral antitumor activity in preclin. leukemia and solid tumor models. Described here are an in vivo cross-resistance profile of penclomedine, treatment schedule dependence studies, and studies exploring the effects of oral drug on human tumors xenografted into mouse brain. The latter studies exploited the apparent facile distribution of penclomedine to the central nervous system. Tumor models used included murine leukemia lines selected in vivo for acquired resistance to various antitumor drugs and the human mammary and lung tumor xenografts MX-1 and H82, resp. The therapeutic effects of oral penclomedine against s.c. MX-1 and H82 xenografts were shown to be independent of treatment schedule. Therapeutic activity was comparable when oral and parenteral treatments were compared. Lines of P388 leukemia resistant to melphalen, cytophosphamide, and carmustine were cross-resistant to penclomedine in vivo. Leukemia lines resistant to antimetabolites, DNA binders/intercalators, and vincristine were not cross-resistant to penclomedine. Intracerebrally implanted MX-1 xenografts retained their sensitivity to oral penclomedine, and therapeutic activity was at least comparable to that of carmustine, a drug known for its ability to cross the blood-brain barrier. These results demonstrate attributes of penclomedine that are relatively uncommon among currently available antitumor drugs and that are of interest for the anticipated clin. development of this drug.

Answer 6:

Bibliographic Information

Use of nude mouse xenografts as preclinical drug screens: in vivo activity of established chemotherapeutic agents against melanoma and ovarian carcinoma xenografts. Taetle, Raymond; Rosen, Fred; Abramson, Ian; Venditti, John; Howell, Stephen. Cancer Cent., Univ. California, San Diego, CA, USA. Cancer Treatment Reports (1987), 71(3), 297-304. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 106:148870 AN 1987:148870 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To evaluate the utility of nude mucosa xenografts as preclin. drug screens, the activity of ten established chemotherapeutic agents was evaluated against seven melanoma and three ovarian carcinoma xenografts. Xenografts were established using primary explants from patients who had not received chemotherapy and serially passaged as s.c. tumors in nude mice. In vivo drug activities for dactinomycin, carmustine, vinblastine, melphalan, amsacrine, cisplatin, bleomycin, mitomycin, doxorubicin, and etoposide were evaluated by 4 weekly i.p. injections of 10% less than LD10 doses. Plots of relative tumor growth vs. time were nearly log-linear. Anal. of in vivo activity was performed using percent control growth (treated/control tumor vol.) and by calcn. of a novel growth delay index obtained by fitting growth curves to a quadratic regression model. Both modes of data anal. identified alkylating agents (melphalan, carmustine, and mitomycin) as the most active drugs against human melanomas. Melphalan, mitomycin, and cisplatin showed the greatest activity against ovarian xenografts. However, complete tumor regressions were noted only with melphalan, mitomycin, and cisplatin against a single ovarian tumor xenograft. Correlation anal. suggested xenograft tumor growth rate was an important determinant of drug response. These results suggest that preclin., new drug screening with melanoma xenografts would identify drugs such as alkylating agents as active, and may not provide an advantage over murine leukemia screens. However, screening with ovarian xenografts may more closely reflect clin. drug activity. Criteria for detecting active drugs in such systems are discussed.

Answer 7:

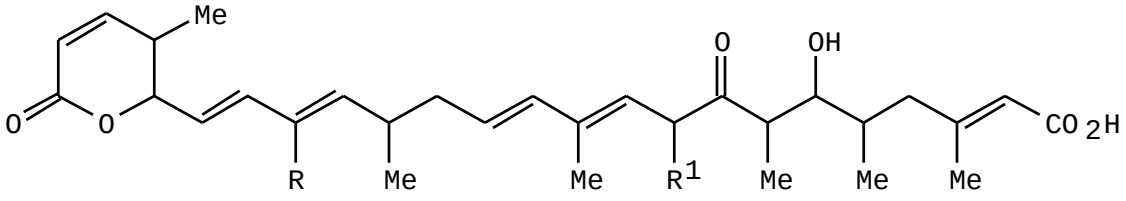
Bibliographic Information

In vivo and in vitro anticancer activity of the structurally novel and highly potent antibiotic CI-940 and its hydroxy analog (PD 114,721). Roberts, Billy J.; Hamelehle, Katherine L.; Sebolt, Judith S.; Leopold, Wilbur R. Warner-Lambert/Parke-Davis

Pharm. Res., Ann Arbor, MI, USA. Cancer Chemotherapy and Pharmacology (1986), 16(2), 95-101. CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 104:218701 AN 1986:218701 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

CI-940 (I) [94730-69-5], NSC 364373 (PD 114,721)(II) [94664-05-8], and PD 118,607 (III) [102490-63-1] demonstrated significant cytotoxic activity in vitro against a no. of human and mouse tumor lines which encompassed a wide range of tissue types. CI-940 retained full activity in vitro against lines of P388 leukemia that are resistant to Adriamycin, amsacrine, and mitoxantrone. Activity was confirmed for both CI-940 and PD 114,721 against a no. of murine exptl. tumor systems in vivo, which included the P388 and L1210 leukemias and also B16 melanoma, Ridgway osteogenic and M5076 sarcomas, and mammary adenocarcinoma 16/C. PD 118,607 was also highly active against B16 melanoma. All 3 agents demonstrated anticancer activity at very low dosages compared with current clin. useful anticancer agents. No significant activity was seen against the MX-1 human mammary xenograft or pancreas 02 tumor models. The primary target for host toxicity of CI-940 and PD 114,721 appeared to be gastrointestinal in nature. Neither CI-940 not PD 114,721 caused delayed lethality when given either i.p. or i.v. In schedule studies, the toxicities of both CI-940 and PD 114,721 were moderately dependent on the regimen used, with total max. tolerated dosages for intermittent, daily, and divided daily dosing schedules of 1, 0.25, and 0.12 mg/kg, resp. .



I, R=Et, R ^{1}=Me

II, R=Et, R ^{1}=CH $_{2}$OH

III, R=R ^{1}=Me

Answer 8:

Bibliographic Information

Correlation between experimentally and clinically demonstrated activity of two new cytotoxic agents in breast cancer. Bailey, M. J.; Smith, I. E. St. George's Hosp., London, UK. Anticancer Research (1985), 5(4), 419-22. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 103:153573 AN 1985:553573 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Exptl. evidence of the cytotoxic activity of 2 new agents was obtained using 5 lines of human breast carcinoma serially transplanted into immunosuppressed mice. Tumor growth delay was used to compare the effect of the new agents with that of cytotoxic drugs of known value in human breast cancer. The mean specific growth delay (no. of tumor vol. doubling times saved) for each agent against the 5 lines was: CL232315 (mitoxantrone) [70476-82-3] 1.9; amsacrine m-AMS [51264-14-3] 0.5; cyclophosphamide, 1.9; adriamycin, 1.8; melphalan 2.2. There was no difference between the activity of mitoxantrone and the clin. useful drugs, but amsacrine was less active than the other agents. A clin. trial of mitorxantrone has confirmed the prediction of useful activity against human breast cancer. Objective responses (CR + PR, UICC response criteria) were noted in 21 out of 70 (30%) patients with advanced breast cancer treated with the drug. The responses were of 4-7 mo plus duration, and the 30% response rate compares favorably with other single agents. Although amsacrine is active in many forms of malignant disease, several phase II studies have shown it to have little effect in breast cancer. By using panels of xenografts of different tumor types it should be possible to select the most appropriate human tumors against which to test a new cytotoxic agent in phase II studies.

Answer 9:

Bibliographic Information

Effect of phase I and II chemotherapeutic agents against human lymphomas heterotransplanted in nude mice. Sordillo, Peter P.; Helson, Christiane; Lesser, Martin; Helson, Lawrence. Sch. Med., Cornell Univ., New York, NY, USA. Oncology (1983), 40(1), 15-17. CODEN: ONCOBS ISSN: 0030-2414. Journal written in English. CAN 98:154964 AN 1983:154964 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Ten chemotherapeutic agents, mostly phase I and II drugs, were tested for activity against 2 human lymphomas heterotransplanted in nude mice. Three of these agents have been tested in phase II trials in patients with lymphoma and found to lack activity; a corresponding lack of activity was found in lymphoma-bearing nude mice. Apart from cyclophosphamide [50-18-0], which is known to have activity against lymphoma and was used as a pos. control, only dianhydrogalactitol (DAG) [23261-20-3] had antitumor activity in the lymphoma-bearing nude mice. Tumor regressions induced by DAG in a heterotransplanted diffuse histiocytic lymphoma were significant.

Answer 10:

Bibliographic Information

Primary and acquired resistance to alkylating agents in heterotransplants of human melanomas and colon carcinomas. Osieka, Rainhardt; Schmidt, Carl G. Innere Klin., West German Tumor Cent., Essen, Fed. Rep. Ger. Proceedings of the International Workshop on Nude Mice (1982), Volume Date 1979, 3rd(Vol. 2), 675-84. CODEN: PIWMDW ISSN: 0171-1784. Journal written in English. CAN 98:119257 AN 1983:119257 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Heterotransplants of human neoplasms onto athymic nude mice was used to screen new antineoplastic agents for activity against specific types of cancer. A variety of agents with diverse mechanisms of action, AMSA (NSC-249992) [51264-14-3], anguidine (NSC-141537) [2270-40-8], Baker's antifol (NSC-139105) [41191-04-2], maytansine (NSC-153858) [35846-53-8], and PALA (NSC-224131) [51321-79-0], were ineffective against a battery of 3 human colon carcinoma heterotransplants and gave few responses against colon carcinoma in phase I and II clin. trials. Screening results also provide the initial basis for anal. of drug resistance mechanisms. Human colon cancer heterotransplant CX-3 (BE) can only be cured by methyl-CCNU [13909-09-6], whereas all other alkylating agents tested were ineffective. In a similar fashion, patterns of resistance to alkylating agents were established for 5 lines of malignant melanoma from patients who received DTIC [4342-03-4], cis-platinum [15663-27-1], and isophosphamide [3778-73-2] either singly or in combination during the course of their treatment. Partial remissions of patients correlated with transient regressions in the heterotransplantation system. With the new method of alk. elution modified for in vivo anal. by use of microfluorometric DNA detns., the development and removal of DNA damage was monitored. Absence of DNA damage at all times correlated with drug resistance. Resistance in a patient previously sensitive to the combination of isophosphamide and cis-platinum was paralleled in the heterotransplantation system. Sensitivity to cis-platinum and isophosphamide was also abolished after 3 transplant generations when initially sensitive tumors that had regrown after treatment with either drug were selected for propagation.

Answer 11:

Bibliographic Information

Molecular pharmacology on human cancer xenografts. Osieka, R.; Becher, R.; Schmidt, C. G. Westdtsch. Tumorzent., Innere Universitaetsklin. Poliklin., Essen, Fed. Rep. Ger. Editor(s): Bastert, Gunther B.; Fortmeyer, Hans Peter; Schmidt-Matthiesen, Heinrich. Thymusaplastic Nude Mice Rats Clincial Oncol., Proc. Symp. (1981), Meeting Date 1979, 513-27. Publisher: Fischer, Stuttgart, Fed. Rep. Ger CODEN: 46XEAJ Conference written in English. CAN 96:115594 AN 1982:115594 CAPLUS

Abstract

The effect of neoplasm inhibitors on human colorectal cancers xenografted into nude mice and on human malignant melanoma heterotransplants is reported. The xenograft system provides 2 advantages over conventional murine tumor models; 1) screening new antineoplastic agents with ref. to specific types of cancer yields information on the spectrum of clin. activity previously available only through phase I-II clin. trials, and 2) with some limitations inherent to biochem. assays on tumor material, mechanisms of primary and acquired resistance can be explored with the system providing the classification into sensitive and resistant tumors and also serving as a source of readily available tumor material. Biochem. studies were limited to the actions of alkylating agents on DNA as their presumptive target mol. In addn. the effect of hyperthermia on human colon cancer xenografts in conjunction with chemotherapy was investigated with specific attention paid to synergism and(or) cross resistance among the 2 modes of treatment.

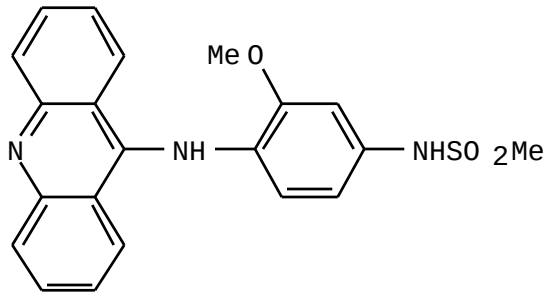
Answer 12:

Bibliographic Information

Effect of 4'-(9-acridinylamino) methanesulfon-m-anisidide (NSC 249992) on human tumor heterotransplants in nude mice. Sordillo, Peter; Helson, Lawrence. Mem. Sloan-Kettering Cancer Cent., New York, NY, USA. Editor(s): Nelson, John D.; Grassi, Carlo. Curr. Chemother. Infect. Dis., Proc. Int. Congr. Chemother., 11th (1980), Meeting Date 1979, 2 1610-11. Publisher: Am. Soc. Microbiol., Washington, D. C CODEN: 43MKAT Conference written in English. CAN 93:88637 AN 1980:488637 CAPLUS

Abstract

The antitumor activity of NSC-249992 (I) [51264-14-3] was tested in nude mice against 6 human tumor heterotransplants, malignant schwannoma, malignant lymphoma, liposarcoma, neuroblastoma, malignant melanoma, and testicular carcinoma. I appeared to be active only against testicular carcinoma and was less active than adriamycin [23214-92-8]. I did not sensitize liposarcoma to radiation therapy. Combined administration of adriamycin and I showed an additive effect, but was also more toxic.



I

Answer 13:

Bibliographic Information

Synthesis and biological activity of stable and potent antitumor agents, aniline nitrogen mustards linked to 9-anilinoacridines via a urea linkage. Kapuriya Naval; Kapuriya Kalpana; Zhang Xiuguo; Chou Ting-Chao; Kakadiya Rajesh; Wu Yu-Tse; Tsai Tung-Hu; Chen Yu-Ting; Lee Te-Chang; Shah Anamik; Naliapara Yogesh; Su Tsann-Long Institute of Biomedical Sciences, Laboratory of Bioorganic Chemistry, Academia Sinica, Taipei 115, Taiwan Bioorganic & medicinal chemistry (2008), 16(10), 5413-23. Journal code: 9413298. E-ISSN:1464-3391. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 18450456 AN 2008338365 MEDLINE

Abstract

To improve the chemical stability and therapeutic efficacy of N-mustard, a series of phenyl N-mustard linked to DNA-affinic 9-anilinoacridines and acridine via a urea linker were synthesized and evaluated for antitumor studies. The new N-mustard derivatives were prepared by the reaction of 4-bis(2-chloroethyl)aminophenyl isocyanate with a variety of 9-anilinoacridines or 9-aminoacridine. The antitumor studies revealed that these agents exhibited potent cytotoxicity in vitro without cross-resistance to taxol or vinblastine and showed potent antitumor therapeutic efficacy in nude mice against human tumor xenografts. It also showed that 24d was capable of inducing marked dose-dependent levels of DNA cross-linking by comet assay and has long half-life in rat plasma.

Answer 14:

Bibliographic Information

Potent antitumor 9-anilinoacridines bearing an alkylating N-mustard residue on the anilino ring: synthesis and biological activity. Bacherikov Valeriy A; Chou Ting-Chao; Dong Hua-Jin; Zhang Xiuguo; Chen Ching-Huang; Lin Yi-Wen; Tsai Tsong-Jen; Lee Rong-Zau; Liu Leroy F; Su Tsann-Long Laboratory of Bioorganic Chemistry, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan Bioorganic & medicinal chemistry (2005), 13(12), 3993-4006. Journal code: 9413298. ISSN:0968-0896. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 15911312 AN 2005268373 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A series of N-mustard derivatives of 9-anilinoacridine was synthesized for antitumor and structure-activity relationship studies. The alkylating N-mustard residue was linked to the C-3' or C-4' position of the anilino ring with an O-ethylene (O-C(2)), O-butylene (O-C(4)), and methylene (C(1)) spacer. All of the new N-mustard derivatives exhibited significant cytotoxicity in inhibiting human lymphoblastic leukemic cells (CCRF-CEM) in culture. Of these agents, (3-(acridin-9-ylamino)-5-{2-[bis (2-chloroethyl)amino]ethoxy}phenyl)methanol (10) was subjected to antitumor studies, resulting in an approximately 100-fold more potent effect than its parent analogue 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA) in inhibiting the growth of human lymphoblastic leukemic cells (CCRF-CEM) in vitro. This agent did not exhibit cross-resistance against vinblastine-resistant (CCRF-CEM/VBL) or Taxol-resistant (CCRF-CEM/Taxol) cells. Remarkably, the therapeutic effect of 10 at a dose as low as one tenth of the Taxol therapeutic dose [i.e., 1-2mg/kg (Q3Dx7) or 3mg/kg (Q4Dx5); intravenous injection] on nude mice bearing human breast carcinoma MX-1 xenografts resulted in complete tumor remission in two out of three mice. Furthermore, 10 yielded xenograft tumor suppression of 81-96% using human T-cell acute lymphoblastic leukemia CCRF-CEM, colon carcinoma HCT-116, and ovarian adenocarcinoma SK-OV-3 tumor models.

Answer 15:

Bibliographic Information

Potent antitumor N-mustard derivatives of 9-anilinoacridine, synthesis and antitumor evaluation. Bacherikov Valeriy A; Chou Ting-Chao; Dong Hua-Jin; Chen Ching-Huang; Lin Yi-Wen; Tsai Tsong-Jen; Su Tsann-Long Laboratory of Bioorganic Chemistry, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan Bioorganic & medicinal chemistry letters (2004), 14(18), 4719-22. Journal code: 9107377. ISSN:0960-894X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15324894 AN 2004418598 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A series of 9-anilinoacridine N-mustard derivatives, in which the alkylating N-mustard residue was linked to the C-3' or C-4' position of the anilino ring with an O-ethylene spacer, was synthesized and evaluated for cytotoxicity against human lymphoblastic leukemic cells (CCRF-CEM) in culture. The results showed that all of the new compounds exhibited potent cytotoxicity with IC(50) values ranging from 0.002 to 0.7 microM, which were as potent or significantly more potent than 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA). Compound 9 did not exhibit cross-resistance against both vinblastine-resistant (CCRF-CEM/VBL) and taxol-resistant (CCRF-CEM/taxol) cells. Additionally, compound 9 demonstrated potent antitumor effect in nude mice bearing human breast carcinoma MX-1 xenografts, resulting in complete tumor remission in two out of three mice at the maximal dose of 1-2mg/kg (Q3Dx7) or 3mg/kg (Q4Dx5) via intravenous injection.

Answer 16:

Bibliographic Information

Preclinical phase II studies in human tumor xenografts: a European multicenter follow-up study. Langdon S P; Hendriks H R; Braakhuis B J; Pratesi G; Berger D P; Fodstad O; Fiebig H H; Boven E ICRF Medical Oncology Unit, Western General Hospital, Edinburgh, UK Annals of oncology : official journal of the European Society for Medical Oncology / ESMO (1994), 5(5), 415-22. Journal code: 9007735. ISSN:0923-7534. Journal; Article; (JOURNAL ARTICLE); (MULTICENTER STUDY); (RESEARCH SUPPORT, NON-U.S. GOV'T); (CLINICAL TRIAL) written in English. PubMed ID 8075048 AN 94355260 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: The EORTC New Drug Development Office has initiated a multicenter collaborative program to evaluate the use of human tumor xenografts to predict phase II clinical activity. A first study confirmed the efficacy of doxorubicin and inactivity of amsacrine against human tumor xenografts (Boven et al., Cancer Res: 52, 5940, 1992). In the follow-up study reported here, the activities of cisplatin, AZQ (diaziquone), pazelliptine and retelliptine have been evaluated against a panel of 40 established tumor lines grown subcutaneously in nude mice. DESIGN: The xenografts used represent carcinomas of the breast, colon, head+neck, ovary, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) and melanoma. Drugs were administered intravenously on days 0 and 7. Doses were for cisplatin 5 mg/kg, AZQ 3-7 mg/kg, pazelliptine 20-80 mg/kg and retelliptine 6-12.5 mg/kg and were selected to give a median loss of about 10%-15% body weight. RESULTS: When activity was defined as a specific growth delay > 1 and a tumor growth inhibition > 50%, then cisplatin demonstrated activity in 15 of 40 xenografts tested (3 of 5 breast, 1 of 6 colon, 0 of 5 head+neck, 2 of 6 NSCLC, 4 of 7 SCLC, 1 of 5 melanoma and 4 of 6 ovarian cancers); AZQ was active in 23 of 38 xenografts (2 of 3 breast, 2 of 7 colon, 4 of 5 head+neck, 3 of 6 NSCLC, 6 of 6 SCLC, 2 of 5 melanoma, 4 of 6 ovarian cancers); pazelliptine was active in 2 of 38 xenografts (1 of 5 breast cancers, 1 of 5 melanoma) while retelliptine was active in 1 of 39 xenografts (a breast cancer xenograft) tested. CONCLUSIONS: These results are reasonably consistent with the clinical activity of cisplatin, but overpredict the clinical efficacy of AZQ. Since pazelliptine and retelliptine are investigational compounds, the clinical phase II studies will provide a prospective test for this model.

The results of the present study and the previous one indicate that the human tumor xenograft model could be suitable for predicting the activity of novel compounds to be developed for treatment of cancer patients.

Answer 17:

Bibliographic Information

(R,R)-2,2'-[1,2-ethanediylbis[imino(1-methyl-2,1-ethanediyl)]]- bis[5-nitro-1H-benz[de]isoquinoline-1,3-(2H)-dione] dimethanesulfonate (DMP 840), a novel bis-naphthalimide with potent nonselective tumoricidal activity in vitro. Kirshenbaum M R; Chen S F; Behrens C H; Papp L M; Stafford M M; Sun J H; Behrens D L; Fredericks J R; Polkus S T; Sipple P; + Research and Development Department, Du Pont Merck Pharmaceutical Company, Glenolden, Pennsylvania 19036 Cancer research (1994), 54(8), 2199-206. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8174127 AN 94228542 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

(R,R)-2,2'-[1,2-ethanediylbis[imino(1-methyl-2,1-ethanediyl)]]- bis[5-nitro-1H-benz[de]isoquinoline-1,3-(2H)-dione] dimethanesulfonate (DMP 840), is a bis-naphthalimide anticancer tumoricidal agent currently in phase I clinical trials. DMP 840 exhibits curative activity in human tumor xenografts, where it shows selectivity for human solid tumors over murine leukemias. In contrast to the selectivity found for DMP 840 in vivo, DMP 840 exhibits potent antiproliferative activity in vitro against a variety of human and murine leukemia and solid tumor cell lines in culture, with inhibitory doses that reduce the number of treated cells to one half (IC50) values ranging from 2.3 to 53 nM. DMP 840 was growth inhibitory to three doxorubicin-resistant cell lines with IC50 values also in the nanomolar range. Clonogenic survival experiments showed that DMP 840 was equally cytotoxic to both exponentially growing and quiescent human clone A colon carcinoma cells. A 1-h incubation of DMP 840 (1.22-12 microM) caused 5-log cell kill in KB-3-1 human epidermoid carcinoma, clone A human colon carcinoma, and L1210 murine leukemia cell lines. The rapid cell killing by DMP 840 in clonogenic survival experiments and initial mechanism of action studies was consistent with a DNA-interactive mechanism for DMP 840 cytotoxicity. Mechanism of action studies in L1210 leukemia cells demonstrated that DMP 840 inhibited the incorporation of thymidine and uridine into DNA and RNA with IC50 values of 0.55 and 0.08 microM, respectively. DMP 840 produced DNA single-strand breaks in a dose-dependent manner. Double-strand breaks were not observed with DMP 840 treatment, even at higher concentrations of compound. Chinese hamster ovary (CHO) and P388 cells resistant to camptothecin and containing a mutant form of topoisomerase I were also used to evaluate whether DMP 840 was cross-resistant with agents active against topoisomerase I.

While the CHOR line was 163-fold resistant to camptothecin, the CHOR line was only 1.7-fold resistant to DMP 840. In summary, DMP 840 is a DNA-interactive agent that demonstrates excellent antiproliferative activity in vitro against cultured tumor cells from both human and murine sources. Its mechanism of tumoricidal activity may be novel.

Answer 18:

Bibliographic Information

Preclinical chemotherapy on human head and neck cancer xenografts grown in athymic nude mice. Braakhuis B J; van Dongen G A; Bagnay M; van Walsum M; Snow G B Department of Otolaryngology and Head and Neck Surgery, Free University Hospital, Amsterdam, The Netherlands Head & neck (1989), 11(6), 511-5. Journal code: 8902541. ISSN:1043-3074. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2584006 AN 90061671 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

This study was undertaken to investigate the potential role of xenografts established from human head and neck squamous cell carcinoma (HNSCC) in the selection of new anticancer agents for phase II clinical trials. Eight HNSCC tumor lines were established in NMRI nude mice. The tumor-bearing animals were then treated with drugs at the maximum tolerated dose level. Treatment with drugs known for their activity in 15%-30% of HNSCC patients [cisplatin (CDDP), bleomycin (BLEO), 5-fluorouracil (5-Fu), cyclophosphamide (CY), and doxorubicin (DOX)] caused strong responses in up to 38% and moderate responses in 50%-67% of the HNSCC tumor lines. Methotrexate (MTX), known to cause remissions in about 40% of HNSCC patients, was only minimally active in this model system. A clinically ineffective drug, amsacrine (m-AMSA), was included as a negative control and showed no or minimal activity in all four HNSCC lines tested. A number of experimental drugs that have promising preclinical activity were also tested. Brequinar sodium (Dup 785) and 10-ethyl, 10-deaza-aminopterin (10-EdAM) showed activity in three of five, and two of the four tested tumor lines respectively. N,N-dimethylformamide (DMF) and 5-aza-2'-deoxycytidine (5-aza-dCyd), agents with the capacity to induce differentiation in in vitro systems, showed moderate activity in 43% and 40%, and strong activity in 14% and 40% of the lines, respectively. Our results indicate that the nude mouse xenograft model may play a role in the screening of new drugs, and in particular, it could be of help in the selection of drugs to be tested in phase II HNSCC clinical trials.

Answer 19:

Bibliographic Information

Preclinical phase II studies in human tumor lines: a European multicenter study. Boven E; Winograd B; Fodstad O; Lobbezoo M W; Pinedo H M Department of Oncology, Free University Hospital, Amsterdam, The Netherlands European journal of cancer & clinical oncology (1988), 24(3), 567-73. Journal code: 8112045. ISSN:0277-5379. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 3383962 AN 88254996 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In an attempt to increase the predictability and to extend the differential capacity of the anticancer drug development program the American National Cancer Institute has recently proposed the introduction of a screening system consisting of human tumor cell lines to select drugs in a disease-oriented fashion rather than by the previously applied drug-oriented strategy. Although this new approach offers great advantages, assay limitations can be identified in testing unknown compounds for antitumor activity in vitro. Human tumor xenografts grown in nude mice may play an additional role in the prediction of clinical activity and the assessment of the spectrum of activity of potential anticancer drugs, because they have a better relationship with the clinical situation of cancer treatment. In a European multicenter collaboration it has been proposed to use panels of human tumor lines from solid tumor types to study: the antitumor activity of three different drugs per tumor type; the reliability of 'preclinical' phase II studies by comparison of the obtained data with results of phase II clinical trials; the feasibility of this joint project, such as the methodology, the reproducibility of experimental data and the introduction of uniform activity criteria. If preclinical phase II studies in human tumor lines generate reliable results, this in vivo screening system will create a unique possibility to better identify promising clinical candidate compounds or analogs of conventional cytostatic agents as well as those tumor types likely to respond to the selected investigational drugs.

Answer 20:

Bibliographic Information

The human tumor cloning assay in cancer research and therapy: a review with clinical correlations. Hanauske A R; Hanauske U; Von Hoff D D Current problems in cancer (1985), 9(12), 1-66. Journal code: 7702986. ISSN:0147-0272. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.); General Review; (REVIEW) written in English. PubMed ID 2419036 AN 86134711 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 21:

Bibliographic Information

Evaluation of 4'-(9-acridinylamino) methanesulfon-m-anisidide (m-AMSA, NSC 249992) on human tumors in nude mice. Sordillo P P; Helson L; Lesser M Cancer clinical trials (1980), 3(4), 385-9. Journal code: 7905482. ISSN:0190-1206. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 6893575 AN 81042555 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The nude mouse human tumor-bearing system is a useful model for studying the efficacy of new drugs against human tumors. A panel of six selected human tumor heterotransplants was used to assess the activity of m-AMSA. No effect was seen against malignant schwannoma, malignant lymphoma, liposarcoma, neuroblastoma, or malignant melanoma. A testicular carcinoma appeared to respond to m-AMSA: however, statistical evaluation demonstrated that this was not significant. No evidence was found to support the use of m-AMSA as a sensitizing agent for radiation.